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Effects of Annual Mass Treatment with Ivermectin for Onchocerciasis on the Prevalence of Intestinal Helminths

Julie Gutman,* Emmanuel Emukah, Njideka Okpala, Chinyere Okoro, Andrew Obasi, Emmanuel S. Miri, and Frank O. Richards, Jr.

Emory University School of Medicine, Division of Pediatric Infectious Diseases, Atlanta, Georgia and Children's Healthcare of Atlanta, Atlanta, Georgia; The Carter Center, Jos, Nigeria; Federal Medical Center, Parasitology Unit, Microbiology Department, Owerri, Imo State, Nigeria; The Carter Center, Atlanta, Georgia

Abstract. We evaluated the effect of annual ivermectin (IV) distribution for onchocerciasis on the prevalence of soil transmitted helminth (STH) infections in school-aged (SAC) and preschool-aged (PAC) children by comparing children in villages that had received treatment for 13 years to those from socioeconomically similar villages in untreated areas. We enrolled 1,031 SAC and 211 PAC for Kato Katz examinations. Treated areas had a lower prevalence of *Ascaris* (SAC: 3% versus 12%, $P < 0.0001$; PAC: 3% versus 10%, $P < 0.051$) and *Trichuris* (SAC: 6% versus 10%, $P = 0.012$; PAC: 1% versus 8%, $P = 0.019$), but not hookworm (SAC: 38% versus 42%, $P = 0.20$; PAC: 21% versus 27%, $P = 0.30$). The prevalence of *Ascaris* or *Trichuris* in treated areas was below the WHO threshold for mass antihelminthic treatment (MDA), but not for hookworm. We conclude that benzimidazole MDA in IV treatment areas is indicated to effectively control hookworm.

INTRODUCTION

The soil transmitted helminths (STH), primarily *Ascaris lumbricoides*, hookworms (*Necator americanus*, and *Ancyclostoma duodenale*), and *Trichuris trichiura*, are highly prevalent in Nigeria, as in most of sub-Saharan Africa.[1–4] They are responsible for significant morbidity and mortality worldwide, causing an estimated loss of 39 million disability adjusted life years (DALYs).[5] This disability burden is greater than that due to malaria (35.7 million DALYs),[5] yet in comparison, STH are among the most neglected of the "neglected tropical diseases." The STH infections disproportionately affect those living in the most resource poor settings, where the infections' effects contribute to the continued cycle of poverty. Although the ultimate goal involves elimination of STH infections through improved hygiene and sanitation, achieving this goal will take time and considerable resources. In the meantime, reductions in morbidity and mortality can be achieved through mass treatment programs, similar to those in place for onchocerciasis and lymphatic filariasis.[6,7] Treatment of intestinal helminths has been shown to have beneficial effects on growth and nutrition, child mortality, and school performance.[8–10]

The most recently published World Health Organization (WHO) guidelines (2006) recommend treatment of all school-aged children (SAC) twice a year in communities where the prevalence of infection exceeds 50% in a sample of SAC, and once a year if the prevalence is 20–50%.[11] With a prevalence of less than 20%, treatment on a case by case basis is recommended.[11] The guidelines also recommend treatment of preschool-aged children (PAC) but do not give guidance on how often. The Global Target put forth by the World Health Assembly Resolution 54.19 in 2001 is that at least 75% of all school-aged children at risk of morbidity from schistosomiasis and STH should be regularly reached and treated by the year 2010. As we have reached this deadline, it is imperative to look at how current programs aimed at other tropical diseases, such as onchocerciasis, may be helping to meet this goal.

Ivermectin (IV) causes paralysis and death of many nematode parasites.[12] It is the drug of choice for onchocerciasis and is routinely used as a mass treatment agent in onchocerciasis and lymphatic filariasis treatment programs, supplied by a generous donation from Merck & Co. Ivermectin was included in the list of WHO recommended drugs[11] for treatment of STH (except hookworms) in 2002, but has since been replaced on the list by the benzimidazole class of anthelmintics.[13] A few studies in humans have shown ivermectin to be efficacious against *Ascaris* (cure rates 78.4–100%)[14–17] and *Strongyloides* (cure rates 83–84%),[15,18] but have had mixed results for the treatment of *Trichuris* (cure rates 11%, 35.2%, 85%)[14,15,17,19] and hookworm (cure rates from 0% to 42%).[15–17,19,20] Previously published studies have shown an initial decrease in prevalence of STH infection immediately following therapy with IV or albendazole, with a gradual rise in prevalence of infection back to baseline over several months to a year.[14,21] A study by Ranque and colleagues[22] using quarterly IV therapy for a year found a significant decrease in the prevalence of STH infection after the first round of therapy, with no subsequent additional decrease. Moncayo and colleagues[23] studied the impact of twice per year IV therapy in northeastern Ecuador on STH. However, no studies have been done to look at the effect on the prevalence of STH following annual mass drug administration (MDA) with IV for onchocerciasis that occurs at approximately 40 million treatments per year in Africa.[24]

The use of annual IV distribution to prevent morbidity caused by onchocerciasis began in Imo state, Nigeria, in 1993 and reached statewide in 1995 following a national onchocereciasis assessment survey that showed high prevalence of onchocerciasis throughout much of southeastern Nigeria.[6,25] This program was begun as a combined effort of the State Ministry of Health, the Lions Clubs, and the River Blindness Foundation. For a time it also received support from the African Program for Onchocerciasis Control (APOC). The distribution program is now run by the State Ministry of Health in conjunction with The Carter Center. Imo State is composed of 27 districts known as local government areas (LGAs). On the basis of the 1995 disease mapping for onchocerciasis, 18 of the 27 LGAs in Imo state receive annual IV therapy because onchocerciasis is a public health problem there. In affected

*Address correspondence to Julie Gutman, Department of Pediatric Infectious Disease, Emory University School of Medicine, 2015 Uppergate Dr. NE, Atlanta, GA 30322. E-mail: gutmanjr@gmail.com

villages, all village members taller than 90 cm are treated annually with a dose (based on height) of approximately 150 mg/kg.[11] The remaining nine LGAs were determined not to have sufficient onchocerciasis prevalence to warrant mass ivermectin treatment. There is no mass treatment programs with benzimidazoles in Imo State directed specifically for STH. Therefore, Imo state provides an ideal setting in which to evaluate the effect of long-term (13 year) annual therapy with ivermectin on the prevalence of STH infections. The important programmatic question to be answered is whether a benzimidazole needs to be added in areas where the African IV-based annual MDA program for onchocerciasis is active to more effectively control STH.

METHODS

Sampling methodology. From July to August, 2008, we performed a cross-sectional survey of STH prevalence in Imo state, Nigeria. We used a stratified sampling procedure to choose 40 villages, 20 treated and 20 untreated villages (Figure 1). We first selected four LGAs of similar ecology (SES, rainfall, soil type); two (Owerri North and Ngor-Okpala) from the areas where all village members taller than 90 cm are offered treatment annually, and two (Ohaji-Egbema and Owerri West) from areas where no systematic anti-parasitic therapy is given, matching villages to be sampled as closely as possible for those factors likely to affect STH prevalence. We selected villages that were rural and poor, having the greatest likelihood of high STH prevalence and being the most similar one to another. In the untreated areas we used a random sampling procedure to select 10 villages in each LGA to be surveyed. There are no school based or mass treatment programs with either IV or benzimidazoles in these villages. In the treated areas, we used the IV treatment coverage figures for the last several years to choose 10 villages in each LGA with the highest ivermectin coverage. Coverage in treated villages averaged 65% of total population (range 24–89%) over the period from 2001 to 2005, improving to 81% (range 73–92%) from 2006 to 2008. In these villages, IV is distributed only by community directed distributors; no school-based distribution programs exist.

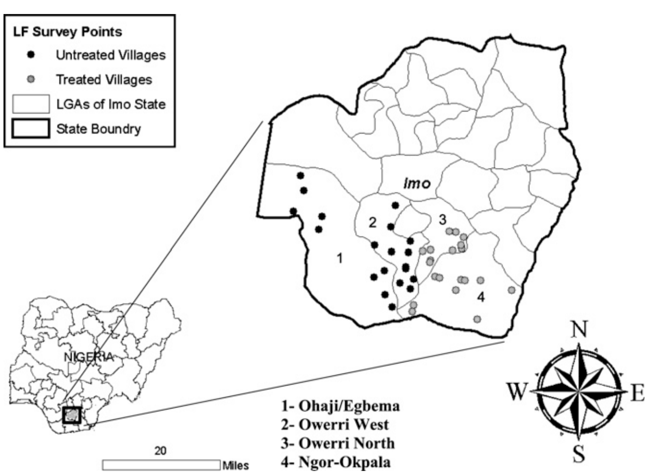

FIGURE 1. Imo State Nigeria, showing treated and untreated local government areas (LGAs) and villages Table 1. Demographic characteristics of untreated and treated children.

Subject enrollment. Two groups of children were enrolled: 1) school-aged children (SAC) from 10 to 16 years of age and 2) preschool-aged children (PAC) who were over 2 years of age and less than 90 cm, to ensure that they had never been treated. Collection cups were distributed to 25–30 SAC to allow (after attrition) for a minimum sample of 25 SAC. Collection cups were distributed up to 10 PAC from each village who fulfilled the enrollment criteria (over 2 years and less than 90 cm); generally, fewer than 10 children meeting these criteria were available. The SAC were accepted for enrollment if they were in primary school grades 4, 5, or 6, or junior secondary (JS) school grades 1, 2, or 3 (equivalent to grades 7, 8, 9). The SAC were excluded from the study if they were less than 10 years or greater than 16 years of age or if they were pregnant. Only one SAC and one PAC from a given household were enrolled. Each child who received a cup had his/her name recorded. The child or child's guardian was instructed to put a walnut sized amount of feces (size showed with a rock) of his or her stool from the next morning into the collection cup using a wooden stick, which was provided. The child/guardian was also instructed to wash his/her hands with soap and water afterwards (noting that this should always be done after defecation). The specimen cups were collected the following day, at which time data were recorded on the survey participant's gender, age, whether the child had taken ivermectin in the previous year, history of passing worms, latrine use, and whether they wore shoes regularly. Height was recorded by measurement against a calibrated pole, weight was recorded using a scale, and mid-arm circumference was measured with a tape measure. All children who returned with stool collection cups were enrolled; those who did not return were called using the previous day's list. If less than 25 children of those who originally received cups failed to deliver samples, additional cups were distributed to those who thought they could provide "on the spot" delivery of fecal specimens until we had collected at least 25 samples from the village. If children did not know their age, it was estimated based on school grade (children entering grade 4 were estimated at 10 years, grade 5 at 11 years, etc. Children who had completed JS3 were estimated at 15 years).

Laboratory methods. The samples were placed in a box with ice packs and returned immediately to the laboratory located at The Carter Center Southeastern Program Office Headquarters in Owerri, Nigeria. Samples were processed by the modified Kato-Katz method[26] within 10 hours of collection, and slides were read within 60 minutes of processing by one of five experienced laboratory technicians by light microscopy (400×). Three slides were prepared from each sample, to increase the likelihood of detecting light infections. Egg counts for *Ascaris*, hookworm, *Trichuris*, and *Schistosoma mansoni* were recorded quantitatively and expressed as eggs per gram (epg) by multiplying the egg counts by 24. The presence of other intestinal helminths was documented qualitatively for each slide. The egg count for each species of parasite was read only from the first slide on which that parasite was found. For quality control, all positive slides were immediately confirmed as positive by a second technician. At the end of the day, slides from 20% of patients were reread by a second technician. The technician performing the quality control at the end of the day was blinded to the results of the first reader. There was never more than 10% difference in egg counts between the first and second reader, and no slides were identified as positive by one reader but negative by the other. Intensity of infection

Table 1
Demographic characteristics of untreated and treated children*

	Untreated	Treated	
SAC	N = 537	N = 494	P value
Mean age, years	12.07 (10–16)	12.01 (10–16)	0.623
Mean height, cm	142.78 (115–173)	142.15 (112–176)	0.364
Mean weight, kg	33.94 (19–66)	33.4 (17–65)	0.305
Mean UAC, cm	19.92 (12.4–29)	19.69 (12.9–27.6)	0.133
Mean BMI	16.41 (11.2–29)	16.27 (10.4–23.5)	0.299
Percent male	51.9% (47.7–56.1%)	49.8% (45.4–54.2%)	0.489
Own a latrine (%)	84.7% (79–90.4%)	91.7% (87.3–96.1%)	0.462
Play barefoot (%)	96.3% (93.8–98.8%)	98.99% (98–99.9%)	0.013
History of worms (%)	48.3% (38.5–58.1%)	33.6% (24.4–42.8%)	0.025
PAC	N = 109	N = 102	P value
Mean age, years	2.1 (2–3)	2.03 (2–3)	0.037
Mean height, cm	84.79 (70–90)	84.43 (70–90)	0.564
Mean weight, kg	10.67 (8–15)	10.62 (1.4–8)	0.805
Mean UAC, cm	14.45 (12.8–18)	14.6 (1.12–12.5)	0.326
Mean BMI	14.86 (10.3–20.8)	14.97 (2.14–11.1)	0.702
Percent male	41.3% (32–50.6%)	52% (42.2–61.7%)	0.122
Own a latrine (%)	76.1% (65.3–87%)	92.2% (85.6–98.7%)	0.007
Play barefoot (%)	100%	95.1% (88.9–100%)	0.025
History of worms (%)	38.5% (24.7–52.4%)	17.6% (8.3–26.9%)	0.009

* SAC = school-aged children; UAC = upper arm circumference; BMI = body mass index; PAC = preschool-aged children.

was defined per WHO guidelines.[27] Infection with *Ascaris* was considered light with < 5,000 epg, moderate with 5,000–49,999 epg, and heavy with ≥ 50,000 epg. Infection with *Trichuris* was considered light with < 1,000 epg, moderate with 1,000– 9,999 epg, and heavy with ≥ 10,000 epg. Infection with hookworm was considered light with < 2,000 epg, moderate with 2,000–3,999 epg, and heavy with ≥ 4,000 epg.

Treatment. All infected children identified during the survey process were treated with 400 mg of albendazole. One child was infected with *S. mansoni* and was treated with praziquantel.

Statistical methods. Data were analyzed with EpiInfo for Windows (CDC, Atlanta, GA) and SAS (version 9.1, Cary, NC). Egg count data were not normally distributed, but were skewed toward low egg counts. For this reason, logarithmic transformation and geometric means were calculated for fecal egg density using antilog-1 where x = number of eggs/gram feces and n the number of persons tested. The non-parametric Kruskal Wallis test was used to test whether the difference in geometric means was significant. For univariate analyses statistical significance was determined using χ^2 test. Multivariate logistic regression was performed using generalized estimating equations and an exchangeable working correlation structure to adjust for correlation within villages. The results of the multivariate logistic regression were reported as odds ratios (OR) and Wald χ^2 P values. Multivariate models for infection with each type of infection were adjusted for gender, residence in a treatment area, playing barefoot, and reported presence of latrine. Data were considered statistically significant with P value < 0.05. Sensitivity, the ability of a test to correctly identify diseased individuals, and specificity, the ability of a test to correctly identify individuals without disease, were calculated for indicators of disease reported by the children.

RESULTS

A total of 1,031 school-aged children and 211 preschool-aged were enrolled: 537 school-aged and 109 preschool-aged from the untreated areas and 494 school-aged and 102 preschool-aged from the treated areas. There was no statistically significant difference in the percent of males in treated and untreated groups. There was no difference in the mean age, height, weight, or arm circumference of the two groups (Table 1). Overall, 46% of surveyed children in the untreated area were infected with intestinal helminths, whereas only 40% of children in the treated areas were infected; this difference was statistically significant (P = 0.024) (Table 2).

School-aged children. Among school-aged children, there was a significant difference in the prevalence of infection with *Ascaris* and *Trichuris* in the treated compared with untreated areas (Table 2). There was no difference in the prevalence of hookworm infection (Table 2). The geometric mean egg count per gram stool was also significantly higher in untreated versus treated MDA samples for *Ascaris* and *Trichuris*, but not for hookworm (*Ascaris*: 1.42 [95% CI 0.97–1.97] versus 0.17 [95% CI 0.08–0.28], P < 0.0001; *Trichuris*: 0.56 [95% CI 0.39–0.76]

Table 2
Prevalence of infection in children in untreated and treated villages

	Untreated	Treated	Total	
All				
N	646	596	1242	P value
Positive	300 (46%)	239 (40%)	539	**0.0243**
Ascaris	78 (12%)	18 (3%)	96	**< 0.0001**
Hookworm	252 (39%)	207 (35%)	459	0.1187
Trichuris	62 (10%)	29 (5%)	91	**0.0014**
School-aged				
N	537	494	1031	P value
Positive	259 (48%)	216 (44%)	475	0.1470
Ascaris	67 (12%)	15 (3%)	82	**< 0.0001**
Hookworm	223 (42%)	186 (38%)	409	0.2039
Trichuris	53 (10%)	28 (6%)	81	**0.0122**
Preschool-aged				
N	109	102	211	P value
Positive	41 (38%)	23 (23%)	64	**0.0174**
Ascaris	11 (10%)	3 (3%)	14	0.0512
Hookworm	29 (27%)	21 (21%)	50	0.3043
Trichuris	9 (8%)	1 (1%)	10	**0.0193**

versus 0.27 [95% CI 0.16–0.38], P = 0.01; hookworm: 7.48 [95% CI 5.76–9.62] versus 5.84 [95% CI 4.43–7.62], P = 0.18). The range of *Ascaris* eggs per gram of stool in untreated versus treated areas was 0–20,760 eggs per gram (epg) compared with 0–5,664 epg, 0–5,208 epg versus 0–312 epg for *Trichuris*, and 0–6,888 versus 0–7,944 for hookworm. In all groups, most of the infections were of light intensity; heavy infections were seen only with hookworm infection. Only one child infected with *Ascaris* had a moderate intensity infection in the treated area (6.7%), compared with 18 (26.9%) with moderate intensity infections in the untreated area (P = 0.07). Only light intensity *Trichuris* infections were seen in the treated areas, whereas 3 children (5.7%) had moderate intensity infections in the untreated area (P = 0.55). Heavy infections with hookworm occurred in 3.2% and 1.8% of children in the treated and untreated area, and moderate intensity infections occurred in 2.1% and 2.7% of children in the treated and untreated area (P = 0.77). Only one child was found to be infected with *S. mansoni*, none were infected with *Schistosoma hematobium.*

Preschool-aged. Among preschool-aged children, who had never received IV even in treated areas, there was a significant difference in the prevalence of infection with *Trichuris* in the treated (1%) compared with untreated areas (8%) (P = 0.019). The difference in the prevalence of *Ascaris* infection approached statistical significance (3% versus 10%, P = 0.051). There was no difference in the prevalence of hookworm infection (21% versus 27%, P = 0.30). Geometric mean egg counts per gram of stool among all children 2–4 years of age were higher in untreated versus treated MDA; this difference was significant for *Ascaris* and *Trichuris* but not for hookworm (*Ascaris*: 0.91 [95% CI 0.30–1.83] versus 0.24 [95% CI 0–0.59], P = 0.04; *Trichuris*: 0.39 [95% CI 0.12–0.73] versus 0.05 [95% CI 0–0.14], P = 0.01; hookworm: 2.44 [95% CI 1.30–4.14] versus 1.74 [95% CI 0.82–3.12], P = 0.36). The range of eggs per gram of stool in untreated versus treated areas was 0–18,648 for *Ascaris*, compared with 0–6,000 in the treated region, 0–312 versus 0–96 for *Trichuris*, and 0–624 versus 0–1,632 for hookworm. Three children had *Ascaris* infection of moderate intensity; one in the treated and two in the untreated areas, respectively (P = 1). The infections with *Trichuris* and hookworm were all of light intensity. There was one case of infection with *S. mansoni.*

Effects of ivermectin on the need for community treatment. From a community perspective, nearly all the villages required at least school-based therapy for hookworm; six of the untreated and four of the treated villages had prevalence of infection > 50% and so qualified for MDA for the entire community (P = 0.597) (Figure 2). None of the treated villages, however, qualified for MDA for either *Ascaris* or *Trichuris*, whereas five and four of the untreated villages qualified for MDA for *Ascaris* and *Trichuris*, respectively (P = 0.047 for *Ascaris* and P = 0.106 for *Trichuris*, *Ascaris* data shown in Figure 3). Of these, one village qualified for community-wide MDA for a prevalence of *Ascaris* > 50%.

Factors contributing to infection. Among SAC, untreated children had a statistically significant increase in the OR for infection for *Ascaris* (P = 0.001) and *Trichuris* (P = 0.024) but not for hookworm (P = 0.5) in univariate analysis (Table 3). Playing barefoot was not associated with a statistically significant change in the OR for any of the infections. There was a slightly higher prevalence of latrines in the treated community, however, this was not found to be statistically different from the untreated communities. Living in a house where there was no latrine was associated with an increased risk of hookworm infection, but not *Ascaris* or *Trichuris* infection. Children who reported always using the latrine had a lower risk of infection with hookworm and *Trichuris* than did children who lived in a house where there was no latrine. Children who reported using the latrine sometimes were similarly protected against hookworm, whereas children who lived in a house with a latrine but reported never using it had no protection from hookworm infection (Table 3). Latrine usage was not associated with a change in infection with *Ascaris*. Similar results were seen when multivariate analysis was used to control for community level similarities (Table 3).

Among untreated PAC, living in a treatment area resulted in a statistically significantly decreased OR for infection for *Ascaris* and *Trichuris*, but not for hookworm, in both univariate and multivariate analysis (Table 4). Among PAC, neither gender nor living in a house with a latrine was significantly associated with infection. Because of the small number of cases of *Trichuris*, we were unable to include the absences of latrine as a factor in the model. Because of the extremely high percent of children who played barefoot (> 95% in all

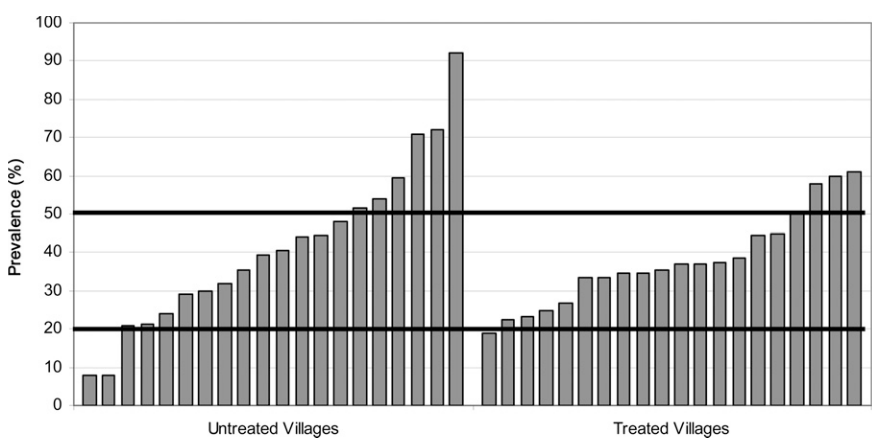

FIGURE 2. Prevalence of hookworm infection among school-aged children by village. This graph shows the prevalence of hookworm infection by village. The black lines indicate the WHO recommended thresholds for school-aged (20%) and community-wide treatment (50%). There was no statistically significant difference in the number of villages requiring mass drug administration (MDA) for hookworm between treated and untreated areas.

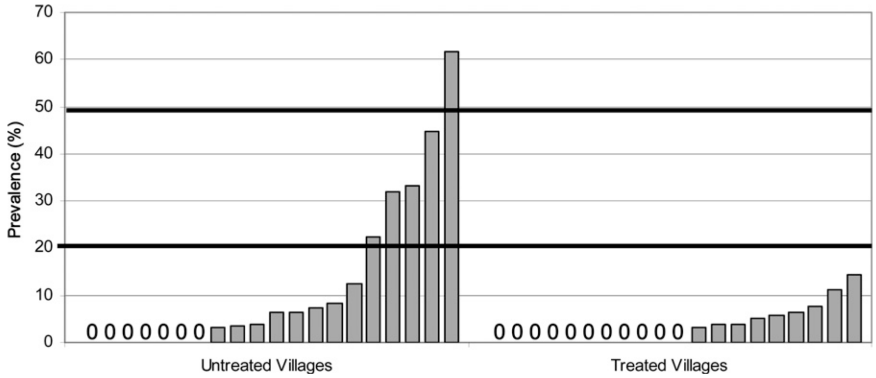

FIGURE 3. Prevalence of *Ascaris* infection among school-aged children by village. This graph shows the prevalence of *Ascaris* infection by village. The zeros represent villages with no infections. The black lines indicate the WHO recommended thresholds for school-aged (20%) and community-wide treatment (50%). The difference in number of villages requiring mass antihelminthic treatment (MDA) between treated and untreated areas was statistically significant.

groups), we were unable to model this risk factor for any of the infections.

History of worms. A history of passing worms was associated with an increased risk of infection, both overall and for each specific type of infection. However, it was neither a sensitive nor specific marker of infection. Overall, sensitivity was 48% and specificity was 67% for detecting any infection; sensitivity was higher when only the untreated group was considered (sensitivity 58%, specificity 63%), but lower in the treated group (sensitivity 35%, specificity 72%). Sensitivity was highest for *Ascaris* infection (sensitivity 64%, specificity 63%). Sensitivity for detection of hookworm and *Trichuris* was similar: for hookworm sensitivity was 48% and specificity was 66%, for *Trichuris* sensitivity was 51% and specificity was 62%. Similar results were obtained if the PACs were excluded.

DISCUSSION

We evaluated the effect of annual IV distribution to prevent morbidity caused by onchocerciasis on the prevalence of STH infections in SAC and PAC by comparing STH prevalence in areas that had received annual treatment of 13 years to untreated areas. Annual community-wide MDA with ivermectin was associated with a decreased prevalence and intensity of infection of both *Ascaris* and *Trichuris* infection in both SAC and PAC, but did not decrease the prevalence or intensity of hookworm infection in either age group. This is in line with previous data showing a poor efficacy of ivermectin against hookworm.[10–14] Although IV treatment did not completely rid the communities of *Ascaris* or *Trichuris*, the prevalence of infection was lowered sufficiently so that all the treated communities were below the WHO recommended threshold for treatment of these parasites. It is interesting to note that MDA clearly affected the force of transmission, because even the PACs, who would never have received IV, had a lower prevalence of infection in the treated areas.

This study showed that hookworm infection remains a public health problem in rural Nigerian communities being treated with IV MDA for onchocerciasis. Annual IV MDA was insufficient to decrease community-wide prevalence of hookworm below WHO mass treatment thresholds. On the basis of our findings, the addition of a benzimidazole to annual IV therapy appears indicated. In addition, an expanded benzimidazole MDA program is needed in areas that are not currently receiving IV MDA for onchocerciasis. Single-dose therapy with albendazole is more effective (72%) than mebendazole (15%) against hookworm.[28] In areas where annual distribution of ivermectin is ongoing, "piggybacking" an additional

TABLE 3
Univariate and multivariate analysis of factors contributing to infection among SACs

	Univariate				Multivariate			
	OR*	Confidence limits		*P* value	OR*	Confidence limits		*P* value
Ascaris								
Untreated	4.44	1.77	11.10	**0.001**	4.25	1.66	10.862	**0.003**
Play barefoot	1.20	0.39	3.70	0.747	1.32	0.55	3.14	0.536
Absence of latrine	1.25	0.86	1.81	0.243	1.22	0.86	1.73	0.260
Male gender	1.59	1.17	2.15	0.003	1.63	1.20	2.20	0.002
Hookworm								
Untreated	1.16	0.75	1.79	0.502	1.07	0.70	1.65	0.743
Play barefoot	0.97	0.52	1.80	0.926	1.01	0.54	1.87	0.974
Absence of latrine	1.76	1.22	2.53	**0.002**	1.76	1.22	2.55	**0.003**
Male gender	1.79	1.37	2.34	< 0.001	1.79	1.35	2.37	< 0.001
Trichuris								
Untreated	1.84	1.08	3.13	**0.024**	1.74	1.02	2.99	**0.043**
Play barefoot	0.62	0.22	1.80	0.384	0.72	0.26	1.98	0.518
Absence of latrine	1.58	0.91	2.76	0.104	1.53	0.86	2.72	0.148
Male gender	1.44	0.99	2.09	0.051	1.42	0.98	2.05	0.063

*SAC = school-aged children; OR = odds ratio.

Table 4
Univariate and multivariate analysis of factors contributing to infection among PACs

	Univariate				Multivariate			
	OR*	Confidence limits		*P* value	OR*	Confidence limits		*P* value
Ascaris								
Untreated	4.38	1.11	17.32	**0.035**	4.22	1.05	16.96	**0.042**
Absence of latrine	1.11	0.22	5.57	0.895	0.95	0.24	3.77	0.954
Male gender	0.55	0.18	1.75	0.313	0.55	0.17	1.73	0.305
Hookworm								
Untreated	1.35	0.64	2.84	0.427	1.17	0.53	2.57	0.699
Absence of latrine	2.10	0.90	4.92	0.086	1.96	0.83	4.62	0.123
Male gender	0.68	0.34	1.34	0.267	0.73	0.37	1.42	0.348
Trichuris								
Untreated	10.31	1.33	80.06	**0.026**	9.46	1.21	74.10	0.032
Male gender	0.56	0.15	2.13	0.393	0.59	0.14	2.44	0.469

* PAC = preschool-aged children; OR = odds ratio.

albendazole tablet into the program would increase the cost per person by the cost of a tablet of albendazole,[27,29,30] and costs related to importation and transports to intervention areas. However, expanding coverage to new areas where piggybacking with other MDA programs could not occur would have a much higher incremental cost as the cost of drug delivery would need to be considered. Twice per year treatments in communities where STH prevalence is > 50% (per WHO recommendations) would dramatically increase costs in both areas.

Moncayo and colleagues[23] conducted a similar study to this one in northeastern Ecuador in areas where IV had been distributed largely on a 6 month (semiannual) schedule as an intervention for onchocerciasis for 15 to 17 years. Their study showed a significant impact only on the prevalence and intensity of infection of *Trichuris*, finding no effect on either *Ascaris* or hookworm infection. This is curious because several studies have shown ivermectin to be efficacious against *Ascaris* (cure rates 78.4–100%).[13–16] They too noted an effect even among PACs who were ineligible for IV therapy, and called, as do we, for the addition of albendazole to the onchocerciasis IV MDA program to enhance impact against STH.

Although other studies have found a significant impact of STH infections on growth and development,[9,31–33] we were unable to show a significant difference in mean height, weight, mid-upper arm circumference, or body mass index (BMI) in the treated versus untreated groups. Although we found a significant impact of ivermetin on the prevalence of *Ascaris* and *Trichuris*, there was no difference in the prevalence or intensity of infection with hookworm in the treated versus untreated areas. The lack of efficacy against hookworm, the STH most associated with causing anemia and intestinal inflammation, explains the lack of difference in growth parameters.

The current WHO guidelines advocate STH treatment of PACs, but provide no specific recommendations as to how often this treatment should be given. In addition, treatment of PACs is not addressed in the World Health Assembly Resolution. Although school-aged children typically have a higher worm burden than preschool-aged children, PACs are still at risk for infection, as shown in our study and others.[3,34–36] Very few studies have been done looking at the negative effects on growth and development in the PAC age group. However, given the rapid rate of development it is conceivable that infections in this age may be more deleterious to subsequent growth and cognitive development than infections suffered in later childhood. The available data shows that deworming of STH-infected PAC improves their health and allows them to reach their cognitive potential.[34,37] Although treatment of SAC may decrease the prevalence in the rest of the community, including in PAC, treatment in this age still appears warranted if age appropriate antihelminthic preparations can be manufactured.

Although intermittent chemotherapy provides a useful tool to combat STH infections, long-term control and eradication of STH infections will require significant improvements in hygiene and sanitation. Reporting consistent latrine use was associated with a decreased rate of infection with both hookworm and *Trichuris*, although not with *Ascaris*. This is in keeping with a study by Sorensen and others,[38] which also found that latrine ownership had more impact on hookworm infection than on *Trichuris* or *Ascaris*. Nguyen and others[39] also found that hookworm infection, but not *Ascaris* or *Trichuris*, was associated with lack of a closed latrine (OR = 2.0). Other studies have found improved sanitation alone to be an insufficient control measure for intestinal helminth infections, but have not noted a differential effect with different intestinal parasites.[40,41]

Reported use of shoes was not associated with a lower prevalence of hookworm infection; although this has previously been reported to be protective against hookworm infection.[42] However, so few children reported shoe use that this finding is probably not noteworthy. In addition, those wearing shoes used "flip-flops," which do not provide much protection from soil, especially in the rainy season.

A history of passing worms was associated with an increased risk of infection, both overall and for each specific type of infection. However, it was neither a sensitive nor specific marker of infection. This suggests that questioning children regarding passing of worms should not be used in place of stool examinations to determine whether villages are in need of treatment of STH.

A weakness of this study was that the baseline level of STH infection in these villages was not obtained before initiating MDA. Although the villages sampled were matched as closely as possible for factors that would be likely to influence the prevalence of STH infection, we cannot be sure that the treated villages had the same initial prevalence and intensity of STH as the untreated villages. However, given the similar hookworm findings between areas, and the known properties of ivermectin against the STHs, we think our assumption that *Ascaris* and *Trichuris* levels were similar before IV interventions began is reasonable.

Further studies are indicated to determine if annual IV and albendazole will suffice to control STHs in IV-treated onchocerciasis areas where STH prevalence is > 50%, so averting the need to invest in an additional treatment round. In addition, preschool-aged children are at risk for STH infections and better studies and age appropriate drug preparations are needed to guide recommendations for STH treatment in this age group.

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Authors' addresses: Julie Gutman, Emory University School of Medicine, Department of Pediatric Infectious Disease, E-mail: gutmanjr@gmail.com. Emmanuel Emukah, Njideka Okpala, and Andrew Obasi, The Carter Center Southeast Programs, Nigeria, E-mails: emukahe@yahoo.com, talk2nj2003@yahoo.com, and andyobasi2@yahoo.com. Chinyere Okoro, Parasitology Unit, Microbiology Department, Federal Medical Center, Owerri, Imo State, Nigeria, E-mail: ihuarulam2002@yahoo.com. Emmanuel S. Miri, The Carter Center Nigeria, Jos, Nigeria, E-mail: emmamiri@yahoo.com. Frank O. Richards, Jr., The Carter Center, Atlanta, GA, E-mail: frich01@emory.edu.

REFERENCES

1. Kirwan P, Asaolu S, Molloy S, Abiona T, Jackson A, Holland C, 2009. Patterns of soil-transmitted helminth infection and impact of four-monthly albendazole treatments in preschool children from semi-urban communities in Nigeria: a double-blind placebo-controlled randomised trial. *BMC Infect Dis 9:* 20.
2. Chan M, 1997. The global burden of intestinal nematode infections—fifty years on. *Parasitol Today 13:* 438–443.
3. Kirwan P, Asaolu SO, Abiona TC, Jackson AL, Smith HV, Holland CV, 2009. Soil-transmitted helminth infections in Nigerian children aged 0–25 months. *J Helminthol 83:* 261–266.
4. Uneke C, Eze KO, Oyibo PG, Azu NC, Ali E, 2007. *Soil-Transmitted Helminth Infection In School Children In South-Eastern Nigeria: The Public Health Implication*. The Internet Journal of Third World Medicine. Volume 4.
5. World Health Organization, 2002. Prevention and Control of Schistosomiasis and Soil Transmitted Helminths: report of a WHO expert committee. World Health Organization Technical Report Series 912.
6. Hopkins D, Eigege S, Miri ES, Gontor I, Ogah G, Umaru J, Gwomkudu CD, Matha W, Jinadu MY, Amadiegwu S, Oyeneka OK, Korve K, Richards F, 2002. Lymphatic filariasis elimination and schistosomiasis control in combination with onchocerciasis control in Nigeria. *Am J Trop Med Hyg 67:* 266–272.
7. Emukah E, Oshuoha E, Miri ES, Onyenama J, Amazigo U, Obijuru C, Osuji N, Ekeanyanwu J, Amadiegwu S, Korve K, Richards FO, 2004. A longitudinal study of impact of repeated mass ivermectin treatment on clinical manifestations of onchocerciasis in Imo State, Nigeria. *Am J Trop Med Hyg 70:* 556–561.
8. Bleakley H, 2003. Diseases and development: evidence from the American South. *J Eur Econ Assoc 1:* 376–386.
9. Stephenson L, Latham MC, Ottesen EA, 2000. Malnutrition and parasitic helminth infections. *Parasitology 121:* S23–S28.
10. Crompton D, Nesheim MC, 2002. Nutritional impact of intestinal helminthiasis during the human life cycle. *Annu Rev Nutr 22:* 35–59.
11. WHO, 2006. *Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers*. Geneva, Switzerland: World Health Organization (WHO).
12. Fox L, 2006. Ivermectin: uses and impact 20 years on. *Curr Opin Inf Dis 19:* 588–593.
13. WHO Partners for Parasite Control. Useful information on schistosomiasis and STH.
14. Belizario V, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, Macatangay BJ, 2003. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. *Bull World Health Organ 81:* 35–42.
15. Marti H, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Ameir JS, Hatz C, 1996. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg 55:* 477–481.
16. Naquira C, Jimenez G, Guerra JG, Bernal R, Nalin DR, Neu D, Aziz M, 1989. Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg 40:* 304–309.
17. Richard-Lenoble D, Kombilia M, Rupp EA, Pappayliou ES, Gaxotte P, Nguiri C, Aziz MA, 1998. Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infections. *Am J Trop Med Hyg 39:* 480–483.
18. Adenusi A, Oke AO, Adenusi AO, 2003. Comparison of ivermectin and thiabendazole in the treatment of uncomplicated human *Strongyloides stercoralis* infection. *Afr J Biotechnol 2:* 465–469.
19. Whitworth J, Morgan D, Maude GH, McNichols AM, Taylor DW, 1991. A field study of the effects of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg 85:* 232–234.
20. Heukelbach J, Winter B, Wilcke T, Muehlen M, Albrecht S, Sales de Oliveira FA, Kerr-Pontes LRS, Liesenfeld O, Feldmeier H, 2004. Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. *Bull World Health Organ 82:* 563–571.
21. Taticheff S, Kebede A, Bulto T, Werkeneh W, Tilahun D, 1994. Effect of ivermectin (Mectizan) on intestinal nematodes. *Ethiop Med J 32:* 7–15.
22. Ranque S, Chippaux JP, Garcia A, Boussinesq M, 2001. Follow-up of *Ascaris lumbricoides* and *Trichuris trichiura* infections in children living in a community treated with ivermectin at 3-monthly intervals. *Ann Trop Med Parasitol 95:* 389–393.
23. Moncayo A, Vaca M, Amorim L, Rodriguez A, Erazo S, Oviedo G, Quinzo I, Padilla M, Chico M, Lovato R, Gomez E, Barreto ML, Cooper PJ, 2008. Impact of long-term treatment with ivermectin on the prevalence and intensity of soil-transmitted helminth infections. *PLoS Negl Trop Dis 2:* e293.
24. 2008. African programme for onchocerciasis control—report on task force meeting, July 2008. *Wkly Epidemiol Rec 83:* 301–312.
25. Gemade E, Jiya JY, Nwoke BE, Ogunba EO, Edeghere H, Akoh JI, Omojola A, 1998. Human onchocerciasis: current assessment of the disease burden in Nigeria by rapid epidemiological mapping. *Ann Trop Med Parasitol 92:* S79–S83.
26. Peters P, El Alamy M, Warren KS, Mahmoud AA, 1980. Quick Kato smear for field quantitation of *Schistosoma mansoni* eggs. *Am J Trop Med Hyg 29:* 217–219.
27. WHO, 2002. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. WHO Technical Report Series 912.
28. Keiser J, Utzinger J, 2008. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA 299:* 1937–1948.
29. Hall A, Horton S, de Silva N, 2009. The costs and cost-effectiveness of mass treatment for intestinal nematode worm infections using different treatment thresholds. *PLoS Negl Trop Dis 3:* e402.
30. Montresor A, Gabrielli AF, Diarra A, Engels D, 2010. Estimation of the cost of large-scale school deworming programmes with benzimidazoles. *Trans R Soc Trop Med Hyg 104:* 129–132.
31. Oberhelman RA, Guerrero ES, Fernandez ML, Silio M, Mercado D, Comiskey N, Ihenacho G, Mera R, 1998. Correlations between intestinal parasitosis, physical growth, and psychomotor devel-

opment among infants and children from rural Nicaragua. *Am J Trop Med Hyg 58:* 470–475.
32. Moore SR, Lima AA, Conaway MR, Schorling JB, Soares AM, Guerrant RL, 2001. Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering. *Int J Epidemiol 30:* 1457–1464.
33. Stephenson LS, Latham MC, Ottesen EA, 2000. Malnutrition and parasitic helminth infections. *Parasitology 121:* S23–S38.
34. Albonico M, Allen H, Chitsulo L, Engels D, Gabrielli AF, Savioli L, 2008. Controlling soil-transmitted helminthiasis in preschool-age children through preventive chemotherapy. *PLoS Negl Trop Dis 2:* e126.
35. Stoltzfus R, Chway HM, Montresor A, Tielsch JM, Jape JK, Albonico M, Savioli L, 2004. Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelminthic treatment improves growth, appetite and anemia in Zanzibari preschool children. *J Nutr 134:* 348–356.
36. Stoltzfus R, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E, 2001. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. *BMJ 323:* 1389–1393.
37. WHO, 2003. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months. WHO: WHO/CDS/CPE/PVC/2002.*4* 2003.
38. Sorensen E, Ismail M, Amarasinghe DK, Hettiarachchi I, De C, Dassenaieke TS, 1994. The effect of the availability of latrines on soil-transmitted nematode infections in the plantation sector in Sri Lanka. *Am J Trop Med Hyg 51:* 36–39.
39. Nguyen P, Nguyen KC, Nguyen TD, Le MB, Bern C, Flores R, Martorell R, 2006. Intestinal helminth infections among reproductive age women in Vietnam prevalence, co-infection and risk factors. *Southeast Asian J Trop Med Public Health 37:* 865–874.
40. Yajima A, Jouquet P, Trung DD, Cam TD, Cong DT, Orange D, Montresor A, 2009. High latrine coverage is not reducing the prevalence of soil-transmitted in Hoa Binh province, Vietnam. *Trans R Soc Trop Med Hyg 103:* 237–241.
41. Asaolu S, Ofoezie IE, Odumuviwa PA, Sowemimo OA, Ogunniyi TA, 2002. Effect of water supply and sanitation on the prevalence and intensity of *Ascaris lumbricoides* among pre-school-age children in Ajebandele and Ifewara, Osun State, Nigeria. *Trans R Soc Trop Med Hyg 96:* 600–604.
42. Chongsuvivatwong V, Pas-Ong S, McNeil D, Geater A, Duerawee M, 1996. Predictors for the risk of hookworm infection: experience from endemic villages in southern Thailand. *Trans R Soc Trop Med Hyg 90:* 630–633.